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## (54) Controlled release dihydrocodeine composition.

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## Description

The present invention relates to a solid, controlled release, oral dosage form containing dihydrocodeine for use in the treatment of moderate to severe pain.

According to the present invention there is provided a solid, controlled release, oral dosage form, the dosage form comprising an analgesically effective amount of dihydrocodeine or a salt thereof in a controlled release matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml. aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 25% and 60% (by wt) dihydrocodeine released after 1 hour, between 45% and 80% (by wt) dihydrocodeine released after 2 hours, between 60% and 90% (by wt) dihydrocodeine released after 3 hours and between 70% and 100% (by wt) dihydrocodeine released after 4 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and such that the peak plasma level of dihydrocodeine obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

USP Paddle Method is the Paddle Method described in US Pharmacopoeia XXI (1985).

In the present specification, "independent of pH" means that the difference, at any given time, between the amount of dihydrocodeine (or a salt) released at pH 1.6 and the amount released at any other pH upto, and including, pH 7.2 (when measured in vitro using the USP Paddle Method at 100rpm in 900ml aqueous buffer) is 5% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

In the present specification, "peak plasma level of dihydrocodeine obtained in vivo" refers to the maximum mean concentration of dihydrocodeine found in the plasma of at least six healthy human volunteers, when the volunteers are subjected to a single dose, pharmacokinetic study.

Preferably the dissolution rate is between 25% and 50% (by wt) dihydrocodeine released after 1 hour, between 45% and 70% after 2 hours, between 60% and 80% after 3 hours and between 70% and 90% after 4 hours.

Most preferably, the dissolution rate is between 30% and 50% (by wt) dihydrocodeine released after 1 hour, between 45% and 65% after 2 hours, between 60% and 75% after 3 hours and between 70% and 85% after 4 hours.

Preferably the peak plasma level of dihydrocodeine is obtained in vivo between 2.25 and 3.75 hours after administration of the dosage form.

When the dihydrocodeine is administered as dihydrocodeine tartrate and the method of dihydrocodeine in plasma analysis is

(i) Extraction from plasma into dichloromethane,

(ii) Extraction from dichloromethane into dilute sulphuric acid, and

(iii) HPLC,

the peak plasma level of dihydrocodeine (per ml. of plasma) is preferably between $1.5 \times 10^{-5}$ and $3 \times 10^{-5}$, most preferably between $2 \times 10^{-5}$ and $3 \times 10^{-5}$, of the amount of dihydrocodeine tartrate administered orally.

Thus, if 60mg of dihydrocodeine tartrate is administered, the peak plasma level of dihydrocodeine is preferably between 90 and 180ngml$^{-1}$, especially between 120 and 180ngml$^{-1}$.

When dihydrocodeine base or a salt other than the tartrate is administered, the preferred ratio of drug administered to peak plasma level of dihydrocodeine must be adjusted according to the molecular weight of the base or salt. By keeping within these narrow ranges for in vitro dissolution rates, the present inventors have surprisingly found that although the present oral dosage forms give peak plasma levels of dihydrocodeine between 2 and 4 hours after administration, they still afford therapeutic levels of dihydrocodeine in vivo over at least a 12 hour period, and can therefore be used on a twice daily basis.

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4-8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of dihydrocodeine, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief.

Most surprisingly, the present inventors have also found that the pain relief obtained with the present formulation is greater than that achieved with normal release formulations giving peak plasma levels (of dihydrocodeine) in the normal period of 1-2 hours after administration.

Furthermore, in the case of the present dosage form, therapeutic levels are generally achieved without concurrent side effects, such as nausea, vomiting, constipation and drowsiness, which are often associated with high blood levels of dihydrocodeine. There is also evidence to suggest that the use of the present dosage forms leads to a reduced risk of drug addiction.

A further advantage of the present composition, which releases dihydrocodeine at a rate that is independent of pH between 1.6 and 7.2 is that it avoids dose dumping upon oral administration. In other words, the dihydrocodeine is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 30 and 180mg, especially between 60 and 120mg, of dihydrocodeine tartrate. Alternatively the dosage form may contain mole equivalent amounts of other dihydrocodeine salts or of the dihydrocodeine base.

The present controlled release matrix may be any matrix that affords in vitro dissolution rates of dihydrocodeine within the narrow ranges required and that releases the dihydrocodeine in a pH independent manner.

Suitable materials for inclusion in the controlled release matrix are

(a) Hydrophilic or hydrophobic polymers, such as gums, cellulose ethers and protein derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic polymer.

(b) Digestible, long chain ($C_8$-$C_{50}$, especially $C_8$-$C_{40}$), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral oils and waxes. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digetible, long chain hydrocarbon.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

One particularly suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one $C_{12}$-$C_{36}$, preferably $C_{14}$-$C_{22}$, aliphatic alcohol and, optionally, at least one polyalkylene glycol.

The at least one hydroxyalkyl cellulose is preferably a hydroxy ($C_1$ to $C_6$) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and especially hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of dihydrocodeine release required. Preferably however, the oral dosage form contains between 2% and 20%, especially between 3% and 12% (by wt) of the at least one hydroxyalkyl cellulose.

The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of dihydrocodeine release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 8% and 40%, especially between 12% and 36% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 8% and 40%, especially between 12% and 36% (by wt) of the total dosage form.

In the present preferred dosage form, the ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the dihydrocodeine from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 1000 and 15000 especially between 1500 and 12000.

In addition to the above ingredients, the controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating dihydrocodeine or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

(a) wet granulating at least one water soluble hydroxyalkyl cellulose with dihydrocodeine or a dihydrocodeine salt to form granules,

(b) mixing the hydroxyalkyl cellulose containing granules with at least one $C_{12}$-$C_{36}$ aliphatic alcohol, and

(c) optionally, compressing and shaping the granules.

In this case the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the hydroxyalkylcellulose.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

Example 1

Dihydrocodeine tartrate (60g) was wet granulated with anhydrous lactose (58.4g) and hydroxyethyl cellulose (20.4g; Natrosol 250 HX, Trade Mark) for 10 minutes and the granules were sieved through a 16 mesh screen. The granules were then dried in a Fluid Bed Dryer at 60 °C.

To the warmed dihydrocodeine containing granules was added molten cetostearyl alcohol (62.2g) and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Talc (2.0g) and magnesium stearate (2.0g) were then added and mixed with the granules. The granules were then compressed into 1000 tablets each containing,

| | mg/tablet |
|---|---|
| Dihydrocodeine Tartrate | 60.0 |
| Anhydrous Lactose | 58.4 |
| Hydroxyethylcellulose | 20.4 |
| Cetostearyl alcohol | 62.2 |
| Talc | 2.0 |
| Magnesium stearate | 2.0 |

Example 2

The procedure of Example 1 was followed except that the quantities of the ingredients were chosen to give 1000 tablets each containing,

| | mg/tablet |
|---|---|
| Dihydrocodeine Tartrate | 120.0 |
| Anhydrous Lactose | 94.0 |
| Hydroxyethylcellulose | 20.0 |
| Cetostearyl alcohol | 60.0 |
| Talc | 3.0 |
| Magnesium stearate | 3.0 |

Example 3

The procedure of Example 1 was followed except that the quantities of the ingredients were chosen to give 1000 tablets each containing,

| | mg/tablet |
|---|---|
| Dihydrocodeine Tartrate | 90.0 |
| Anhydrous Lactose | 40.5 |
| Hydroxyethylcellulose | 22.5 |
| Cetostearyl Alcohol | 67.5 |
| Talc | 4.5 |
| Magnesium Stearate | 3.75 |

Example 4

The procedure of Example 1 was followed except that the quantities of the ingredients were chosen to give 1000 tablets each containing.

| | mg/tablet |
|---|---|
| Dihydrocodeine Tartrate | 120.0 |
| Anhydrous Lactose | 54.0 |
| Hydroxyethylcellulose | 30.0 |
| Cetostearyl Alcohol | 90.0 |
| Talc | 6.0 |
| Magnesium Stearate | 5.0 |

Example 5

The procedure of Example 1 was repeated except that the wet granulation step proceeded for 12 minutes.

Example 6

The procedure of Example 1 was repeated except that the wet granulation step proceeded for 16 minutes.

In Vitro Dissolution Studies

A. In vitro dissolution studies were conducted on tablets prepared as described in Example 1. The dissolution method was the USP Paddle Method described in US Pharmacopoeia XXI (1985). The paddle speed was 100 rpm, the temperature was 37 °C and the solution was

(a) 900 ml. aqueous buffer (pH 1.6)
(b) 900 ml. aqueous buffer (pH 4.6)
(c) 900 ml. aqueous buffer (pH 6.5, USP buffer), and
(d) 900 ml. aqueous buffer (pH 7.2).

The amount of dihydrocodeine tartrate released was analysed by uv spectrophotometry (at 284nm). Results are given in Table 1.

TABLE 1

| Time (hr) | wt. % Dihydrocodeine Tartrate released | | | |
|---|---|---|---|---|
| | pH 1.6 | pH 4.6 | pH 6.5 | pH 7.2 |
| 1 | 43.8 | 43.6 | 43.9 | 44.1 |
| 2 | 63.4 | 62.1 | 62.5 | 63.1 |
| 3 | 76.7 | 75.1 | 75.4 | 77.6 |
| 4 | 86.3 | 85.0 | 84.8 | 87.4 |
| 5 | 92.1 | 91.3 | 91.5 | 93.8 |
| 6 | 94.9 | 94.6 | 94.9 | 97.6 |
| 7 | 95.9 | 96.3 | 96.3 | 99.7 |
| 8 | 96.0 | 96.7 | 97.5 | 100.0 |
| 9 | 96.3 | 97.0 | 98.2 | 100.5 |
| 10 | 96.3 | 97.0 | 98.9 | 100.6 |

B. Similar in vitro studies were conducted on tablets prepared as described in Example 3, but using 900ml aqueous buffer (pH 6.5, USP buffer) only.

Results are given in Table 2.

TABLE 2

| Time (hr) | Wt. % Dihydrocodeine Tartrate released |
|---|---|
| 1 | 38.6 |
| 2 | 55.8 |
| 3 | 68.5 |
| 4 | 78.7 |
| 5 | 86.5 |
| 6 | 92.6 |
| 7 | 96.7 |
| 8 | 99.2 |

C. Similar in vitro studies were conducted on tablets prepared as described in Example 4, but using 900ml aqueous buffer (pH 6.5, USP buffer) only.

Results are given in Table 3.

TABLE 3

| Time (hr) | Wt. % Dihydrocodeine Tartrate released |
|---|---|
| 1 | 31.9 |
| 2 | 48.6 |
| 3 | 60.9 |
| 4 | 70.9 |

D. Similar in vitro studies were conducted on tablets prepared as described in Example 5, but using 900ml aqueous buffer (pH 6.5, USP buffer) only.

Results are given in Table 4.

TABLE 4

| Time (hr) | Wt. % Dihydrocodeine Tartrate released |
|---|---|
| 1 | 42.1 |
| 2 | 60.6 |
| 3 | 73.6 |
| 4 | 83.7 |
| 5 | 91.2 |
| 6 | 96.5 |
| 7 | 99.3 |

Clinical Studies

A. A single dose, randomised, comparative, pharmacokinetic study was conducted on 6 subjects employing,

i) A controlled release dihydrocodeine tartrate tablet prepared as described in Example 1, (a 60mg dose), and

ii) 2 x 30mg Dihydrocodeine tartrate tablets (DF118: Trade Mark; a 60mg dose).

Analysis of the plasma samples for dihydrocodeine was performed as follows:

(a) Extraction of the plasma sample with dichloromethane,

(b) Extraction of the dichloromethane layer with dilute sulphuric acid, and

(c) HPLC analysis of the acidic layer.

Results are given in Table 5

TABLE 5

| Time (hr) | Mean Plasma Conc. (ng ml) | |
|---|---|---|
| | Example 1 | DF118 |
| 0.25 | - | 7 |
| 0.50 | - | 80 |
| 0.75 | - | 160 |
| 1.0 | 62 | 205 |
| 1.25 | - | 177 |
| 1.50 | - | 194 |
| 2.0 | 108 | 183 |
| 3.0 | 130 | 137 |
| 4.0 | 111 | 119 |
| 5.0 | 114 | - |
| 6.0 | 110 | 73 |
| 8.0 | 85 | 51 |
| 10.0 | 63 | 31 |
| 12.0 | 34 | 23 |
| 14.0 | 27 | - |
| 24.0 | 6 | - |

B. A phase III open randomised comparative cross-over study was conducted on 54 patients employing
(i) Controlled release dihydrocodeine tartrate (60mg) tablets prepared as described in Example 5. and
(ii) Dihydrocodeine tartrate (30mg) normal release tablets (DF118. Trade Mark),
in the control of moderate to severe pain in osteoarthritis.

On recruitment into the study, patients were randomly allocated to receive either controlled release or normal release tablets for 3 weeks. Patients were then "crossed over" to receive the alternative analgesic for a further 3 weeks. The starting dose in all cases was 120mg dihydrocodeine tartrate per day, either one controlled release tablet taken twice a day or one normal release tablet taken four times a day.

At the end of the first week, the dose could be doubled to 240mg dihydrocodeine tartrate per day, either two controlled release tablets taken twice a day or two normal release tablets taken four times a day, if pain control at the starting dose was unsatisfactory and side effects were not a problem.

Patients were crossed over to the second study medication on a mg. for mg. basis.

The patients were assessed for severity of pain (on a scale 0 (no pain) to 5 (severe pain)) both on entry to the study and at the end of each three week period.

Results of the pain assessment are given in Table 6.

TABLE 6

| | | Baseline | Normal Release DHC Tartrate | Controlled Release DHC Tartrate |
|---|---|---|---|---|
| Pain scores for Completing Patients | 0 | 0 | 1 | 1 |
| | 1 | 5 | 4 | 9 |
| | 2 | 26 | 26 | 23 |
| | 3 | 15 | 7 | 5 |
| | 4 | 7 | 1 | 1 |
| | 5 | 1 | 0 | 0 |
| Non-Completing Patients | | 0 | 15 | 15 |
| Total | | 54 | 54 | 54 |

Using the Wilcoxon matched pairs signed rank test (see Non-parametric statistics for the behavioural sciences. S Siegel. 1956), it was found that the difference between the categorical pain scores for baseline and controlled release tablets reached much greater significance ($p<0.01$) than the difference between the baseline and normal release tablets ($p<0.05$).

The patients were also assessed for severity of pain by the visual analogue score (VAS) method. Results are given in Table 7.

TABLE 7

| | Baseline | Normal Release DHC Tartrate | Controlled Release DHC Tartrate |
|---|---|---|---|
| Patients Completing the study | 54 | 39 | 38 |
| VAS | 55.4 | 42.5 | 38.3 |

## Claims

**Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. A solid, controlled release, oral dosage form, the dosage form comprising an analgesically effective amount of dihydrocodeine or a salt thereof in a controlled release matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 25% and 60% (by wt) dihydrocodeine released after 1 hour, between 45% and 80% (by wt) dihydrocodeine released after 2 hours, between 60% and 90% (by wt) dihydrocodeine released after 3 hours and between 70% and 100% (by wt) dihydrocodeine released after 4 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of dihydrocodeine obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

2. A dosage form according to claim 1 characterised in that the in vitro dissolution rate is between 25% and 50% (by weight) dihydrocodeine released after 1 hour, between 45% and 70% (by weight) dihydrocodeine released after 2 hours, between 60% and 80% (by weight) dihydrocodeine released after 3 hours and between 70% and 90% (by weight) dihydrocodeine released after 4 hours, preferably between 30% and 50% (by weight) dihydrocodeine released after 1 hour, between 45% and 65% (by weight) dihydrocodeine released after 2 hours, between 60% and 75% (by weight) dihydrocodeine released after 3 hours and between 70% and 85% (by weight) dihydrocodeine released after 4 hours.

3. A dosage form according to either claim 1 or claim 2 characterised in that the peak plasma level of dihydrocodeine occurs between 2.25 and 3.75 hours after administration of the dosage form.

4. A dosage form according to any one of claims 1 to 3 characterised in that an analgesically effective amount of a dihydrocodeine salt comprises between 30 and 180mg, preferably between 60 and 120mg, of dihydrocodeine tartrate.

5. A dosage form according to any one of claims 1 to 4 characterised in that the controlled release matrix comprises at least one water soluble hydroxyalkyl, preferably $C_1$ to $C_6$ alkyl, cellulose, at least one $C_{12}$ to $C_{36}$, preferably $C_{14}$ to $C_{22}$, aliphatic alcohol and, optionally, at least one polyalkylene glycol, preferably polyethylene glycol.

6. A dosage form according to any one of claims 1 to 5 characterised in that the at least one hydroxyalkyl cellulose comprises hydroxypropyl cellulose, hydroxypropylmethylcellulose or, preferably, hydroxyethylcellulose.

7. A dosage form according to either claim 5 or claim 6 characterised in that the dosage form contains between 2% and 20% (by weight), especially between 3% and 12% (by weight), of the at least one hydroxyalkylcellulose.

8. A dosage form according to any one of claims 5 to 7 characterised in that the aliphatic alcohol comprises lauryl alcohol, myristyl alcohol, stearyl alcohol or, preferably, cetyl alcohol or cetostearyl alcohol.

9. A dosage form according to any one of claims 5 to 8 characterised in that the dosage form contains between 8% and 40%, preferably between 12% and 36%, (by weight) of the at least one fatty alcohol or of the at least one fatty alcohol and the at least one polyalkylene glycol.

10. A dosage form according to any one of claims 5 to 9 characterised in that the ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol:polyalkylene glycol is between 1:2 and 1:4, preferably between 1:3 and 1:4.

**Claims for the following Contracting States : AT, ES, GR**

1. A process for the preparation of a solid, controlled release, oral dosage form characterised by incorporating an analgesically effective amount of dihydrocodeine or a salt thereof in a controlled release matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100rpm in 900ml aqueous buffer (pH between 1.6 and 7.2) at 37 °C is between 25% and 60% (by wt) dihydrocodeine released after 1hour, between 45% and 80% (by wt) dihydrocodeine released after 2 hours, between 60% and 90% (by wt) dihydrocodeine released after 3 hours and between 70% and 100% (by wt) dihydrocodeine released after 4 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of dihydrocodeine obtained in vivo occurs between 2 and 4 hours after administration of the dosage form.

2. A process according to claim 1 characterised in that the in vitro dissolution rate is between 25% and 50% (by weight) dihydrocodeine released after 1 hour, between 45% and 70% (by weight) dihydrocodeine released after 2 hours, between 60% and 80% (by weight) dihydrocodeine released after 3 hours and between 70% and 90% (by weight) dihydrocodeine released after 4 hours, preferably between 30% and 50% (by weight) dihydrocodeine released after 1 hour, between 45% and 65% (by weight) dihydrocodeine released after 2 hours, between 60% and 75% (by weight) dihydrocodeine released after 3 hours and between 70% and 85% (by weight) dihydrocodeine released after 4 hours.

3. A process according to either claim 1 or claim 2 characterised in that the controlled release matrix comprises at least one water soluble hydroxyalkyl, preferably $C_1$ to $C_6$ alkyl, cellulose, at least one $C_{12}$ to $C_{36}$, preferably $C_{14}$ to $C_{22}$, aliphatic alcohol and, optionally, at least one polyalkylene glycol, preferably polyethylene glycol.

4. A process according to any one of claims 1 to 3 characterised in that the at least one hydroxyalkyl cellulose comprises hydroxypropyl cellulose, hydroxypropylmethylcellulose or, preferably hydroxyethylcellulose.

5. A process according to either claim 3 or claim 4 characterised in that the dosage form contains between 2% and 20% (by weight), especially between 3% and 12% (by weight), of the at least one hydroxyalkylcellulose.

6. A process according to any one of claims 3 to 5 characterised in that the aliphatic alcohol comprises lauryl alcohol, myristyl alcohol, stearyl alcohol or, preferably, cetyl alcohol or cetostearyl alcohol.

7. A process according to any one of claims 3 to 6 characterised in that the dosage form contains between 8% and 40%, preferably between 12% and 36%, (by weight) of the at least one fatty alcohol or of the at least one fatty alcohol and the at least one polyalkylene glycol.

8. A process according to any one of claims 3 to 7 characterised in that the ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol:polyalkylene glycol is between 1:2 and 1:4, preferably between 1:3 and 1:4.

9. A process according to claim 1 characterised by

(a) wet granulating at least one water soluble hydroxyalkyl cellulose with dihydrocodeine or a dihydrocodeine salt to form granules.
(b) mixing the hydroxyalkyl cellulose containing granules with at least one $C_{12}$-$C_{36}$ aliphatic alcohol, and
(c) optionally, compressing and shaping the granules

10. A process according to claim 9 characterised in that the at least one water soluble hydroxyalkyl cellulose and the dihydrocodeine or the dihydrocodeine salt are wet granulated with water, the weight ratio of the water to the dry weight of the at least one water soluble hydroxyalkyl cellulose being between 1.5 to 1 and 5 to 1, especially between 1.75 to 1 and 3.5 to 1.

**Patentansprüche**

**Patentansprüche für folgenden Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Feste, orale Dosierungsform mit kontrollierter Freisetzung, wobei die Dosierungsform eine analgetisch wirksame Menge von Dihydrocodein oder einem Salz hiervon in einer Matrix für kontrollierte Freisetzung umfaßt, worin die Auflösungsrate der Dosierungsform in vitro, gemessen nach der USP Rührer-Methode bei 100 Upm in 900 ml wässrigem Puffer (pH zwischen 1,6 und 7,2) bei 37° C zwischen 25 % und 60 % (in Gewicht) nach 1 h freigesetztes Dihydrocodein, zwischen 45 % und 80 % (in Gewicht) nach 2 h freigesetztes Dihydrocodein, zwischen 60 % und 90 % (in Gewicht) nach 3 h freigesetztes Dihydrocodein und zwischen 70 % und 100 % (in Gewicht) nach 4 h freigesetztes Dihydrocodein beträgt, wobei die Freisetzungsrate in vitro vom pH zwischen 1,6 und 7,2 unabhängig ist und so ausgewählt ist, daß der in vivo erzielte Spitzenplasmapegel von Dihydrocodein zwischen 2 und 4 h nach Applikation der Dosierungsform auftritt.

2. Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die Auflösungsrate in vitro zwischen 25 % und 50 % (in Gewicht) nach 1 h freigesetztes Dihydrocodein, zwischen 45 % und 70 % (in Gewicht) nach 2 h freigesetztes Dihydrocodein, zwischen 60 % und 80 % (in Gewicht) nach 3 h freigesetztes Dihydrocodein und zwischen 70 % und 90 % (in Gewicht) nach 4 h freigesetztes Dihydrocodein, bevorzugt zwischen 30 % und 50 % (in Gewicht) nach 1 h freigesetztes Dihydrocodein, zwischen 45 % und 65 % (in Gewicht) nach 2 h freigesetztes Dihydrocodein, zwischen 60 % und 75 % (in Gewicht) nach 3 h freigesetztes Dihydrocodein und zwischen 70 % und 85 % (in Gewicht) nach 4 h freigesetztes Dihydrocodein, beträgt.

3. Dosierungsform nach Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß der Spitzenplasmapegel des Dihydrocodeins zwischen 2.25 und 3.75 h nach Applikation der Dosierungsform auftritt.

4. Dosierungsform nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß eine analgetisch wirksame Menge eines Dihydrocodeinsalzes zwischen 30 und 180 mg, bevorzugt zwischen 60 und 120 mg, Dihydrocodeintartrat ausmacht.

5. Dosierungsform nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß die Matrix mit kontrollierter Freisetzung wenigstens eine wasserlösliche Hydroxyalkyl-, bevorzugt $C_1$- bis $C_6$-Alkylcellulose, wenigstens einen aliphatischen $C_{12}$-bis $C_{36}$-, bevorzugt $C_{14}$- bis $C_{22}$-Alkohol und, wahlweise, wenigstens ein Polyalkylenglykol, bevorzugt Polyethylenglykol, umfaßt.

6. Dosierungsform nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß die wenigstens eine Hydroxyalkylcellulose Hydroxypropylcellulose, Hydroxypropylmethylcellulose oder, bevorzugt, Hydroxyethylcellulose, umfaßt.

7. Dosierungsform nach Anspruch 5 oder Anspruch 6, dadurch gekennzeichnet, daß die Dosierungsform zwischen 2 % und 20 % (in Gewicht), insbesondere zwischen 3 % und 12 % (in Gewicht), der wenigstens einen Hydroxyalkylcellulose enthält.

8. Dosierungsform nach einem der Ansprüche 5 bis 7, dadurch gekennzeichnet, daß der aliphatische Alkohol Laurylalkohol, Myristylalkohol, Stearylalkohol oder, bevorzugt, Cetylalkohol oder Cetostearylalkohol umfaßt.

9. Dosierungsform nach einem der Ansprüche 5 bis 8, dadurch gekennzeichnet, daß die Dosierungsform zwischen 8% und 40 %, bevorzugt zwischen 12 % und 36 %, (in Gewicht) des wenigstens einen Fettalkohols und des wenigstens einen Polyalkylenglykols enthält.

10. Dosierungsform nach einem der Ansprüche 5 bis 9, dadurch gekennzeichnet, daß das Verhältnis der wenigstens einen Hydroxyalkylcellulose zu dem wenigstens einen aliphatischen Alkohol-Polyalkylenglykol zwischen 1 : 2 und 1 : 4, bevorzugt zwischen 1 : 3 und 1 : 4, liegt.

**Patentansprüche für folgenden Vertragsstaaten: AT, ES, GR**

1. Verfahren zur Herstellung einer festen, oralen Dosierungsform mit kontrollierter Freisetzung, gekennzeichnet durch Inkorporieren einer analgetisch wirksamen Menge von Dihydrocodein oder eines Salzes hiervon in einer Matrix mit kontrollierter Freisetzung, worin die Auflösungsrate der Dosierungsform in vitro, gemessen nach der USP Rührer-Methode bei 100 Upm in 900 ml wässrigem Puffer (pH zwischen 1.6 und 7.2) bei 37° C zwischen 25 % und 60 % (in Gewicht) nach 1 h freigesetztes Dihydrocodein, zwischen 45 % und 80 % (in Gewicht) nach 2 h freigesetztes Dihydrocodein, zwischen 60 % und 90 % (in Gewicht) nach 3 h freigesetztes Dihydrocodein und zwischen 70 % und 100 % (in Gewicht) nach 4 h freigesetztes Dihydrocodein beträgt, wobei die Freisetzungsrate in vitro vom pH zwischen 1.6 und 7.2 unabhängig ist und so ausgewählt ist, daß der in vivo erzielte Spitzenplasmapegel von Dihydrocodein zwischen 2 und 4 h nach Applikation der Dosierungsform auftritt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Auflösungsrate in vitro zwischen 25 % und 50 % (in Gewicht) nach 1 h freigesetztes Dihydrocodein, zwischen 45 % und 70 % (in Gewicht) nach 2 h freigesetztes Dihydrocodein, zwischen 60 % und 80 % (in Gewicht) nach 3 h freigesetztes Dihydrocodein und zwischen 70 % und 90 % (in Gewicht) nach 4 h freigesetztes Dihydrocodein, bevorzugt zwischen 30 % und 50 % (in Gewicht) nach 1 h freigesetztes Dihydrocodein, zwischen 45 % und 65 % (in Gewicht) nach 2 h freigesetztes Dihydrocodein, zwischen 60 % und 75 % (in Gewicht) nach 3 h freigesetztes Dihydrocodein und zwischen 70 % und 85 % (in Gewicht) nach 4 h freigesetztes Dihydrocodein, beträgt.

3. Verfahren nach Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß die Matrix für die kontrollierte Freisetzung wenigstens eine wasserlösliche Hydroxyalkyl-, bevorzugt C$_{1}$- bis C$_{6}$-Alkylcellulose, wenigstens einen aliphatischen C$_{12}$- bis C$_{36}$-, bevorzugt C$_{14}$- bis C$_{22}$-Alkohol und, wahlweise, wenigstens ein Polyalkylenglykol, bevorzugt Polyethylenglykol, umfaßt.

4. Verfahren nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß die wenigstens eine Hydroxyalkylcellulose Hydroxypropylcellulose, Hydroxypropylmethylcellulose oder, bevorzugt, Hydroxyethylcellulose, umfaßt.

5. Verfahren nach Anspruch 3 oder Anspruch 4, dadurch gekennzeichnet, daß die Dosierungsform zwischen 2 % und 20 % (in Gewicht), insbesondere zwischen 3 % und 12 % (in Gewicht), der wenigstens einen Hydroxyalkylcellulose enthält.

6. Verfahren nach einem der Ansprüche 3 bis 5, dadurch gekennzeichnet, daß der aliphatische Alkohol Laurylakohol, Myristylalkohol, Stearylalkohol oder, bevorzugt, Cetylalkohol oder Cetostearylalkohol umfaßt.

7. Verfahren nach einem der Ansprüche 3 bis 6, dadurch gekennzeichnet, daß die Dosierungsform zwischen 8% und 40 %, bevorzugt zwischen 12 % und 36 %, (in Gewicht) des wenigstens einen Fettalkohols und des wenigstens einen Polyalkylenglykols enthält.

8. Verfahren nach einem der Ansprüche 3 bis 7, dadurch gekennzeichnet, daß das Verhältnis der wenigstens einen Hydroxyalkylcellulose zu dem wenigstens einen aliphatischen Alkohol-Polyalkylenglykol zwischen 1 : 2 und 1 : 4, bevorzugt zwischen 1 : 3 und 1 : 4, liegt.

9. Verfahren nach Anspruch 1, gekennzeichnet durch:
(a) Naßgranulieren wenigstens einer wasserlöslichen Hydroxyalkylcellulose mit Dihydrocodein oder einem Dihydrocodeinsalz zur Bildung von Granulen.

(b) Mischen der Hydroxyalkylcellulose enthaltenden Granulen mit wenigstens einem aliphatischen $C_{12}$-$C_{36}$-Alkohol, und

(c) wahlweise Pressen und Formen der Granulen.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß die wenigstens eine wasserlösliche Hydroxyalkylcellulose und das Dihydrocodein oder das Dihydrocodeinsalz mit Wasser naßgranuliert werden, wobei das Gewichtsverhältnis des Wassers zu dem Trockengewicht der wenigstens einen wasserlöslichen Hydroxyalkylcellulose zwischen 1,5 zu 1 und 5 zu 1, insbesondere zwischen 1,75 zu 1 und 3,5 zu 1, liegt.

**Revendications**

**Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

1. Forme d'administration orale solide à libération contrôlée, la forme d'administration comprenant une quantité de dihydrocodéine ou d'un de ses sels efficace au point de vue analgésique dans une matrice pour libération contrôlée dans laquelle la vitesse de dissolution in vitro de la forme d'administration, lorsqu'elle est mesurée par la méthode par palettes de l'USP à 100 tpm dans 900 ml de tampon aqueux (pH entre 1.6 et 7.2) à 37 °C se situe entre 25% et 60% (en poids) de dihydrocodéine libérés après une heure, entre 45% et 80% (en poids) de dihydrocodéine libérés après 2 heures, entre 60% et 90% (en poids) de dihydrocodéine libérés après 3 heures et entre 70% et 100% (en poids) de dihydrocodéine libérés après 4 heures, la vitesse de libération in vitro étant indépendante du pH entre pH 1.6 et 7.2 et choisie de telle manière que le pic du taux plasmatique de la dihydrocodéine obtenu in vivo se présente entre 2 et 4 heures après l'administration de la forme d'administration.

2. Forme d'administration selon la revendication 1, caractérisée en ce que la vitesse de dissolution in vitro se situe entre 25% et 50% (en poids) de dihydrocodéine libérés après 1 heure, entre 45% et 70% (en poids) de dihydrocodéine libérés après 2 heures, entre 60% et 80% (en poids) de dihydrocodéine libérés après 3 heures et entre 70% et 90% (en poids) de dihydrocodéine libérés après 4 heures, de préférence entre 30% et 50% (en poids) de dihydrocodéine libérés après 1 heure, entre 45% et 65% (en poids) de dihydrocodéine libérés après 2 heures, entre 60% et 75% (en poids) de dihydrocodéine libérés après 3 heures et entre 70% et 85% (en poids) de dihydrocodéine libérés après 4 heures.

3. Forme d'administration selon l'une quelconque des revendications 1 et 2, caractérisée en ce que le pic du taux plasmatique de la dihydrocodéine se présente entre 2.25 et 3.75 heures après l'administration de la forme d'administration.

4. Forme d'administration selon l'une quelconque des revendications 1 à 3, caractérisée en ce que une quantité efficace au point de vue analgésique d'un sel de dihydrocodéine comprend entre 30 et 180 mg, de préférence entre 60 et 120 mg de tartrate de dihydrocodéine.

5. Forme d'administration selon l'une quelconque des revendications 1 à 4, caractérisée en ce que la matrice pour libération contrôlée comprend au moins une hydroxyalkyl - de préférence alkyl en $C_1$-$C_6$ - cellulose soluble dans l'eau, au moins un alcool aliphatique en $C_{12}$ à $C_{36}$, de préférence $C_{14}$ à $C_{22}$ et, facultativement, au moins un polyalkylène glycol, de préférence du polyéthylène glycol.

6. Forme d'administration selon l'une quelconque des revendications 1 à 5, caractérisée en ce que la (les) hydroxyalkyl cellulose(s) comprend (comprennent) de l'hydroxypropyl cellulose, de l'hydroxypropylméthylcellulose, ou de préférence, de l'hydroxyéthylcellulose.

7. Forme d'administration selon l'une quelconque des revendications 5 ou 6, caractérisée en ce que la forme d'administration contient entre 2% et 20% (en poids), spécialement entre 3% et 12% (en poids) d'hydroxyalkylcellulose(s).

8. Forme d'administration selon l'une quelconque des revendications 5 à 7, caractérisée en ce que l'alcool aliphatique comprend de l'alcool laurylique, de l'alcool myristylique, de l'alcool stéarylique ou, de préférence, de l'alcool cétylique ou de l'alcool cétostéarylique.

9. Forme d'administration selon l'une quelconque des revendications 5 à 8, caractérisée en ce que la forme d'administration contient entre 8% et 40%, de préférence entre 12% et 36% (en poids) d'alcool(s) gras ou d'alcool(s) gras et de polyalkylène glycol(s).

10. Forme d'administration selon l'une quelconque des revendications 5 à 9, caractérisé en ce que le rapport hydroxyalkyl cellulose(s) sur alcool(s) aliphatique(s) polyalkylène glycol(s) est entre 1:2 et 1:4 de préférence entre 1:3 et 1:4.

**Revendications pour les Etats contractants suivants : AT, ES, GR**

1. Procédé pour la préparation d'une forme d'administration orale solide à libération contrôlée, caractérisé en ce qu'on incorpore une quantité de dihydrocodéine ou d'un de ses sels efficace au point de vue analgésique dans une matrice pour libération contrôlée dans laquelle la vitesse de dissolution in vitro de la forme d'administration, lorsqu'elle est mesurée par la méthode par palettes de l'USP à 100 tpm dans 900 ml de tampon aqueux (pH compris entre 1.6 et 7.2) à 37°C se situe entre 25% et 60% (en poids) de dihydrocodéine libérés après une heure, entre 45% et 80% (en poids) de dihydrocodéine libérés après 2 heures, entre 60% et 90% (en poids) de dihydrocodéine libérés après 3 heures et entre 70% et 100% (en poids) de dihydrocodéine libérés après 4 heures, la vitesse de libération in vitro étant indépendante du pH entre pH 1.6 et 7.2 et choisie de telle manière que le pic du taux plasmatique de la dihydrocodéine obtenu in vivo se présente entre 2 et 4 heures après l'administration de la forme d'administration.

2. Procédé selon la revendication 1, caractérisé en ce que la vitesse de dissolution in vitro se situe entre 25% et 50% (en poids) de dihydrocodéine libérés après 1 heure, entre 45% et 70% (en poids) de dihydrocodéine libérés après 2 heures, entre 60% et 80% (en poids) de dihydrocodéine libérés après 3 heures et entre 70% et 90% (en poids) de dihydrocodéine libérés après 4 heures, de préférence entre 30% et 50% (en poids) de dihydrocodéine libérés après 1 heure, entre 45% et 65% (en poids) de dihydrocodéine libérés après 2 heures, entre 60% et 75% (en poids) de dihydrocodéine libérés après 3 heures et entre 70% et 85% (en poids) de dihydrocodéine libérés après 4 heures.

3. Procédé selon la revendication 1 ou la revendication 2, caractérisé en ce que la matrice pour libération contrôlée comprend au moins une hydroxyalkyl - de préférence alkyl en $C_1$-$C_6$ - cellulose solubie dans l'eau, au moins un alcool aliphatique en $C_{12}$ à $C_{36}$, de préférence $C_{14}$ à $C_{22}$ et, facultativement, au moins un polyalkylène glycol, de préférence du polyéthylène glycol.

4. Procédé selon l'une quelconque des revendications 1 à 3, caractérisé en ce que la (les) hydroxyalkylcellulose(s) comprend (comprennent) de l'hydroxypropyl- cellulose, de l'hydroxypropylméthyl-cellulose, ou de préférence, de l'hydroxyéthylcellulose.

5. Procédé selon l'une quelconque des revendications 3 et 4, caractérisé en ce que la forme d'administration contient entre 2% et 20% (en poids), spécialement entre 3% et 12% (en poids) d'hydroxyalkylcellulose.

6. Procédé selon l'une quelconque des revendications 3 à 5, caractérisé en ce que l'alcool aliphatique comprend de l'alcool laurylique, de l'alcool myristylique, de l'alcool stéarylique ou, de préférence, de l'alcool cétylique ou de l'alcool cétostéarylique.

7. Procédé selon l'une quelconque des revendications 3 à 6, caractérisé en ce que la forme d'administration contient entre 8% et 40%, de préférence entre 12% et 36% (en poids) d'alcool(s) gras ou d'alcool(s) gras et de polyalkylène glycol(s).

8. Procédé selon l'une quelconque des revendications 3 à 7, caractérisé en ce que le rapport hydroxyalkyl cellulose(s) sur alcool(s) aliphatique(s) polyalkylène glycol(s) est entre 1:2 et 1:4, de préférence entre 1:3 et 1:4.

9. Procédé selon la revendication 1, caractérisé en ce que:
(a) on granule par voie humide au moins une hydroxyalkyl cellulose soluble dans l'eau avec de la dihydrocodéine ou un sel de dihydrocodéine pour former des granules:

(b) on mélange les granules contenant l'hydroxyalkylcellulose avec au moins un alcool aliphatique en $C_{12}$ - $C_{36}$ et
(C) facultativement, on comprime et on met en forme les granules.

**10.** Procédé selon la revendication 9, caractérisé en ce que l'hydroxyalkylcellulose soluble dans l'eau et la dihydrocodéine ou le sel de dihydrocodéine sont granulés par voie humide avec de l'eau, le rapport en poids de l'eau sur le poids sec d'hydroxyalkylcellulose(s) étant entre 1.5 sur 1 et 5 sur 1, spécialement entre 1.75 sur 1 et 3.5 sur 1.